BJP British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2012.01940.x
www.brjpharmacol.org

REBUTTAL

Ecstasy cannot be assumed to be 3,4-methylenedioxyamphetamine (MDMA)

LINKED ARTICLES

This is a rebuttal by the authors (Green *et al.*, pp. 1523–1536 of this issue) to a commentary by Parrott, pp. 1518–1520 of this issue. To view the article by Green *et al.* visit http://dx.doi.org/10.1111/j.1476-5381.2011.01819.x. To view the commentary by Parrott visit http://dx.doi.org/10.1111/j.1476-5381.2012.01941.x

We thank Prof Parrott (Parrott 2012) for his interest in our review (Green *et al.*, 2012). Our main aim was to discuss the problems that arise in interpreting data obtained when administering 3,4-methylenedioxymethamphetamine (MDMA) to experimental animals in terms of possible clinical consequences and *vice versa*, not to disparage the evidence that Ecstasy is neurotoxic in humans. We presented evidence that the pharmacokinetics of MDMA in rats and primates are fundamentally different from the pharmacokinetics of the drug in humans. Because the plasma half-life of the drug in rats is 10 times shorter than in humans, the acute adverse events in rats may be minimal compared with those in humans, and this includes body temperature and endocrine changes. Conversely, the rapid metabolism of the drug in rats to form neurotoxic metabolites may result in more severe long-term effects in that species than those that may occur in humans.

We had no intention of suggesting that there was no evidence for some recreational Ecstasy users presenting with evidence of 5-HT neurotoxicity, albeit it is clear from the literature that some of this evidence remains open to several interpretations. What we did claim was that pure 3,4-methylenedioxymethamphetamine (MDMA) taken alone was *unlikely* to cause 5-HT neurotoxicity in man. Here we must emphasize the term MDMA, as it is crucial to our discussion. Parrott, in contrast, uses the term 'Ecstasy/MDMA' several times when discussing neurotoxicity (Parrott, 2012). This association of Ecstasy with MDMA is one of the major problems of translation that we addressed. The Ecstasy tablet that most recreational users buy and ingest is not necessarily MDMA. Indeed, in many cases, it clearly is not. The tablet is often adulterated with other compounds, and one investigation identified no less than 14 substances other than MDMA in Ecstasy tablets, which users nevertheless presumably believed contained only MDMA (Vogels *et al.*, 2009). Many of the adulterants identified were also psychoactive and included compounds structurally related to MDMA such as 3,4-methylenedioxyethylamphetamine and 2-methylamino-1-(3,4-methylenedioxyphenyl)butane, which have poorly researched pharmacology and toxicology. In addition, most recreational users of Ecstasy also knowingly ingest other psychoactive compounds such as alcohol and cannabis. Alcohol, for example, alters the pharmacokinetics of MDMA (Hamida *et al.*, 2009). While, as Parrott states, clinical studies have attempted to allow for these confounding factors in any examination of the physical and psychological effects of MDMA in humans, such analysis is always limited not only by the other compounds the evaluators are unaware of, but also drugs perhaps not even considered to be relevant by the user and therefore not disclosed. It is unlikely that coffee and 'energy drinks' such as Red Bull are always disclosed, but there is now good preclinical evidence that caffeine, which incidentally has also been found as an adulterant in Ecstasy tablets, enhances both the hyperthermia and neurotoxicity induced in rats by MDMA (Camarasa *et al.*, 2006; Vanattou-Saïfoudine *et al.*, 2010). And this brings us to the crux of the problem and weakness of all the clinical data cited by Parrott (2012). A basic tenet of all good clinical pharmacology is accurate knowledge of the doses administered, frequency of administration and any confounding factors such as other drugs being consumed. None of these data are available with any precision in the clinical studies quoted. Of course one has some indication as to dose (although as Vogels *et al.*, (2009) reported, the dose contained in illicitly obtained tablets is highly variable) and frequency of drug ingestion, but this information is generally obtained from the user whose recall is likely to be limited or who decides to obfuscate. Crucially, the information can never take into account the problem of drug tablet adulteration. The fact that hair or urine samples detect MDMA merely shows the user has consumed the drug, not how much or when or what other drugs were taken concurrently.

We never suggested that MDMA exposure was not going to be associated with physical or psychological change. However such changes are not necessarily associated with long-term neurotoxic damage. We have shown that

long-term behavioural effects can occur in rats both with and without 5-HT neurotoxicity (Fone *et al.*, 2002; Bull *et al.*, 2003; Rodsiri *et al.*, 2011). It is interesting that Parrott approvingly quotes the Verheyden *et al.* (2003) study in support of his contention that neurotoxic damage has occurred. Because this study noted that the majority of persons reporting chronic psychiatric problems reported 'improved mental health' after quitting the drug, this surely allows us to conclude that the drug had produced subacute changes rather than any that could be associated with long-term neurotoxic damage.

A further limitation to any clinical study is that one cannot perform prospective studies with the aim of investigating whether long-term neurotoxic events occur, so weaknesses arise with regard to any psychological abnormalities observed. Are persons with high risk of psychiatric problems more likely to misuse the drug, or does the drug induce changes in high-risk individuals? If high risk also happened to be associated with 5-HT abnormalities in the brains, then any conclusion that MDMA has induced neurotoxicity is spurious.

We most certainly did not suggest that MDMA acted as a neurotoxin only under conditions of severe hyperthermia as is stated by Parrot in his sixth paragraph (Parrott, 2012). We have been involved in many studies on the effects of MDMA on body temperature in rats (see Docherty and Green, 2010) including one that demonstrated that neurotoxicity can occur in the absence of hyperthermia (O'Shea *et al.*, 1998) and another that showed that hyperthermia worsens neurotoxic damage (Green *et al.*, 2004). In our review, what we did propose was that because of the very different pharmacokinetics of MDMA in rats and humans, it is probable that humans would suffer serious or fatal adverse events at plasma levels below those likely to be required to induce 5-HT neurotoxicity.

We emphasize again that we are not denying the clinical observations reviewed by Parrott, but conclude that the effects seen cannot be ascribed solely to the effects of MDMA, as he seems to be proposing. We also repeat our contention that MDMA in combination with other drugs may induce neurotoxicity and this could be said to be supported by the clinical studies quoted by Parrott.

Finally, we can but assume that Parrott concurs with our principal conclusion that 'the doses currently being used to investigate the possible therapeutic benefits of MDMA are unlikely to produce any severe acute or importantly any long-term neurotoxic damage in the human brain' as he used such a dose (100 mg or approximately 1.4 mg·kg $^{-1}$) in one of his recent studies in human volunteers (Parrott *et al.*, 2011).

Conflict of interest

The authors declare no conflict of interest.

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References

Bull EJ, Hutson PH, Fone KCF (2003). Reduced social interaction following 3,4-methylenedioxymethamphetamine (MDMA) is not associated with enhanced 5-HT_{2C} receptor responsivity. Neuropharmacology 44: 439–448.

Camarasa J, Pubill D, Escubedo E (2006). Association of caffeine to MDMA does not increase antinociception but potentiates adverse effects of this recreational drug. Brain Res 1111: 72–82.

Docherty JR, Green AR (2010). The role of monoamines in the changes in body temperature induced by 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) and its derivatives. Br J Pharmacol 160: 1029–1044.

Fone KCF, Beckett SRG, Topham IA, Swettenham J, Ball M, Maddock L (2002). Long-term changes in social interaction and reward following repeated MDMA administration to adolescent rats without accompanying serotonergic neurotoxicity. Psychopharmacology 159: 437–444.

Green AR, Sanchez V, O'Shea E, Saadat KS, Elliott JM, Colado MI (2004). Effect of ambient temperature and a prior neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA) on the hyperthermic response of rats to a single or repeated ('binge' ingestion) low dose of MDMA. Psychopharmacology 173: 264–269.

Green AR, King MV, Shortall SE, Fone KCF (2012). Lost in translation: preclinical studies on 3,4-methylenedioxymethamphetamine provide information on mechanisms of action, but do not allow accurate prediction of adverse events in humans. Br J Pharmacol 166: 1523–1536.

Hamida SB, Tracqui A, de Vasconcelos AP, Szwarc E, Lazarus C, Kelche C *et al.* (2009). Ethanol increases the distribution of MDMA to the rat brain: possible implications in the ethanol-induced potentiation of the psychostimulant effects of MDMA. Int J Neuropsychopharmacol 12: 749–759.

O'Shea E, Granados R, Esteban B, Colado MI, Green AR (1998). The relationship between the degree of neurodegeneration of rat brain 5-HT nerve terminals and the dose and frequency of administration of MDMA ('ecstasy'). Neuropharmacology 37: 919–926.

Parrott AC, Gibbs A, Scholey AB, King R, Owens K, Swann P *et al.* (2011). MDMA and methamphetamine: some paradoxical negative and positive mood changes in an acute dose laboratory study. Psychopharmacology 215: 527–536.

Parrott AC, (2012). MDMA and 5-HT neurotoxicity: the empirical evidence for its adverse effects in humans – no need for translation. Br J Pharmacol 166: 1518–1520.

Rodsiri R, Spicer C, Green AR, Marsden CA, Fone KCF (2011). Acute concomitant effects of MDMA binge dosing on extracellular 5-HT, locomotion and body temperature and the long-term effect on novel object discrimination in rats. Psychopharmacology 213: 365–376.

Vanattou-Saïfoudine N, McNamara R, Harkin A (2010). Mechanisms mediating the ability of caffeine to influence MDMA ('Ecstasy')-induced hyperthermia in rats. Br J Pharmacol 160: 860–877.

Verheyden SL, Maidment R, Curran HV (2003). Quitting ecstasy: an investigation of why people stop taking the drug and their subsequent mental health. J Psychopharmacol 17: 371–378.

Vogels N, Brunt TM, Rigter S, van Dijk P, Vervaeke H, Niesink RJ (2009). Content of ecstasy in the Netherlands: 1993–2008. Addiction 104: 2057–2066.